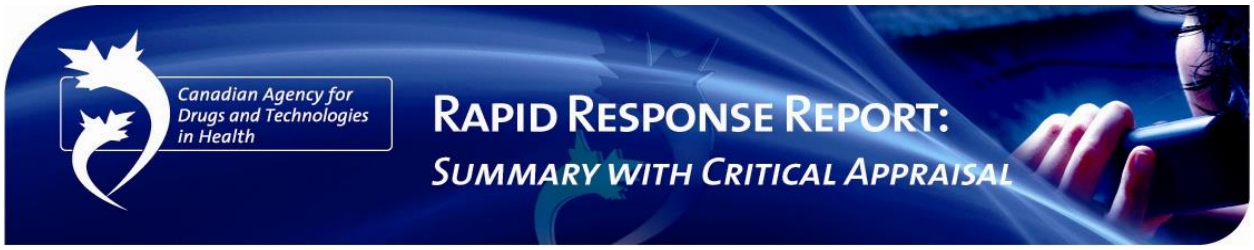

TITLE: Biological Mesh: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines – An Update

DATE: 11 August 2015

CONTEXT AND POLICY ISSUES

A variety of products are available for use as surgical reconstructive materials including biological mesh, absorbable synthetic mesh, and non-absorbable synthetic mesh. Biological meshes are acellular extracts, also known as acellular dermal matrix (ADM) obtained from human (allografts) or non-human (xenografts) sources. Sources of biological mesh include human dermis or fascia lata, porcine dermis or intestine, and bovine dermis or pericardium. It has been suggested that biological mesh products have advantages over synthetic mesh by reducing the risk of infection or rejection;[1] however, the retail cost of biological meshes is high.[2] It is important to clarify whether evidence of significant clinical and cost-effectiveness of biological meshes has been demonstrated to warrant their widespread adoption in surgical practice. CADTH had previously reviewed the evidence for the clinical and cost-effectiveness of biological meshes for a variety of indications, as well as the evidence-based guidelines for their use.[3] However, that report concluded that there was insufficient evidence to clearly establish the place in therapy of biological mesh products. Therefore, there is remaining uncertainty regarding the optimal use of biological mesh in surgical procedures.

The purpose of this report is to update the existing clinical and cost-effectiveness evidence, as well as the evidenced-based guidelines regarding the use of biological mesh products.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of biological mesh products?

2. What is the cost-effectiveness of biological mesh products?

3. What are the evidence-based guidelines regarding appropriate clinical indications for biological mesh products?

4. What are the evidence-based guidelines regarding the use of biological mesh products?

KEY FINDINGS

Evidence regarding the clinical effectiveness and safety of biological mesh was generally positive or neutral; however, the majority of publications concluded that there is insufficient high quality evidence to preferentially support the use of biological mesh products. Some recommendations for their use in hernia repair were identified. Biological mesh may be more cost-effective than no mesh for hernia repair and post-mastectomy breast reconstruction but results from these cost-effectiveness analyses should be interpreted with caution due to limitations in model assumptions. Overall, there is insufficient evidence to suggest the optimal place in therapy for biological mesh products.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and July 14, 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients of any age
Intervention	Biological mesh products (also known as ADM)
Comparator	Q1 and 2: Synthetic mesh, any comparator, no comparator Q3 and 4: No comparator
Outcomes	Q1: Clinical effectiveness outcomes (e.g., rate of re-injury or recurrence, length of hospitalization); Safety (e.g., post-operative complications [e.g., seroma]) Q2: Cost-effectiveness outcomes (e.g., ICER, QALY) Q3: Evidence-based guidelines regarding indications for biological mesh products Q4: Evidence-based guidelines regarding the use of biological mesh products
Study Designs	Health technology assessments, systematic reviews, economic evaluations, evidence-based guidelines

ADM = acellular dermal matrix; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, they exclusively contained studies also in another included systematic review, they were systematic reviews with a single author therefore omitting the possibility of duplicate selection and data extraction to minimize bias, or were published prior to 2010. Economic evaluations that did not conduct a cost-effectiveness or cost-utility analysis were excluded. Guidelines that did not provide a description of their methodology, and those lacking a formal literature search or a system to evaluate the strength of the evidence and recommendations were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR,[4] economic studies were assessed using the Drummond checklist,[5] and guidelines were assessed with the AGREE II instrument.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 505 citations were identified in the literature search. Following screening of titles and abstracts, 470 citations were excluded and 35 potentially relevant reports from the electronic search were retrieved for full-text review. Ten potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 21 publications were excluded for various reasons, while 24 publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Due to the volume of relevant literature identified, clinical evidence was limited to systematic reviews (SRs). Randomized controlled trials (RCTs) of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Seventeen SRs were identified regarding the clinical effectiveness of biological mesh products for the following indications: abdominal wall reconstruction or hernia repair,[7-12] pelvic organ prolapse,[13-15] head and neck reconstruction,[16-18] upper and lower extremity wound repair,[19] breast reconstruction,[20] perineal reconstruction,[21] and multiple indications.[22] Years of publication ranged from 2010 to 2015 (with literature searches, when provided, up to 2014 for the most recent review), and the total number of included studies ranged from five to 311. The identified SRs included comparative evidence (e.g., RCTs, prospective and retrospective non-randomized studies),[7,8,13,14,16,17,21] non-comparative evidence (e.g., case series, case reports),[9-12,15,22] or a

combination of both.[18-20,23] There was some overlap in the studies included in the SRs regarding the same indication (hernia repair, vaginal prolapse repair, head and neck reconstruction).

Three economic evaluations were included in this report regarding the cost-effectiveness of biological mesh products; all were cost-utility analyses. One study evaluated Strattice biological mesh compared with no mesh for ventral hernia repair[2] and two evaluated AlloDerm biological mesh compared with either no mesh or autologous dermal flaps for breast reconstruction.[24,25] All three analyses were conducted with a third-party payer perspective. The hernia repair study assumed that the average patient age was 50 years, permanent mesh was not an option, surgical techniques used were fairly uniform, and that early and late complications resolved within 30 days and three months, respectively.[2] Both breast reconstruction studies assumed that the average patient age at surgery was 45 years and life expectancy was 81.1 years, there was a six month recovery time for mastectomy flap necrosis, and a one month recovery time for other complications.[24,25] Medicare reimbursement codes (e.g., for surgical procedures, treatment of complications, and biological mesh costs) as well as manufacturer retail costs for the biological mesh were used for the economic model cost inputs in all three studies.

Four relevant evidence-based guidelines regarding the clinical indications for and use of biological mesh were identified.[1,26-28] Of these, three guidelines[26-28] stated that SRs were performed and one guideline[1] reported that a literature search was performed. All guidelines provided levels of evidence according to an evidence hierarchy, and strength of the stated recommendations. Grading scales of the included guidelines are provided in Appendix 5. Recommendations were consensus based for all four guidelines.

Country of Origin

The SRs were conducted by authors based in the United States,[8-10,12,18,19,23] Canada,[20,22] the United Kingdom,[15,21] China,[14,16,17] Australia,[13] Germany,[7] and the Netherlands.[11]

The three economic evaluations[2,24,25] were conducted in the United States.

Two evidence-based guidelines were identified from the National Institute for Health and Care Excellence (NICE) in the United Kingdom[27] and the American Academy of Orthopedic Surgeons (AAOS) in the United States.[28] The other two evidence-based guidelines were produced by international groups: the Committee on Pelvic Organ Prolapse Surgery (lead author from Australia),[1] and the International Endohernia Society (lead author from Germany).[26]

Patient Population

The patient populations varied by the surgical indication addressed by each of the included studies and guidelines.

Patient populations of the SRs selected for this review included:

- Patients undergoing surgical revision of hiatal[7] or incisional/ventral[8,10,11] hernia, and abdominal wall reconstruction[9,12]
- Patients undergoing surgical repair of vaginal[13,14,23] or rectal[15] prolapse
- Patients undergoing parotidectomy[16,17] or general head and neck reconstruction[18]
- Patients undergoing post-mastectomy breast reconstruction[20]

- Patients with non–burn-related, traumatic, chronic extremity wounds[19]
- Patients undergoing perineal reconstruction[21]
- Mixed population of patients who have had a surgical procedure (multiple indications) using AlloDerm biological mesh[22]

Patient populations of the included economic evaluations were:

- Patients undergoing ventral hernia repair with component separation[2]
- Patients undergoing two-stage, expander–implant-based[24] or single-stage, implant-based[25] immediate breast reconstruction following mastectomy

The identified guidelines concerned the following patient populations:

- Patients with abdominal wall hernias[26]
- Patients with pelvic organ prolapse[1]
- Women with urinary incontinence[27]
- Adults with diagnosed osteoarthritis of the glenohumeral joint[28]

Interventions and Comparators

All of the included studies focused on biological mesh products as the intervention. Some specified the studied type of mesh by brand name or by species of origin. The biological meshes derived from human, bovine, and porcine sources that were evaluated in the included SRs and cost-utility analyses are listed in Table 2.

Table 2: Biological Mesh Products Evaluated in the Included Systematic Reviews and Economic Evaluations

Human-Derived	Porcine-Derived	Bovine-Derived
Alloderm[8-12,17,18,20,22,24,25]	Permacol[8,9,11,12,15,21]	Veritas[9,10]
FlexHD[10]	Surgisis[8-11,21]	SurgiMend[10,12]
GraftJacket[19]	Strattice[2,8-10]	Zyplast[18]
Renov[18]	CollaMend[9,10]	Integra[19]
Tutoplast[13]	Pelvicol[13,14]	Tutomesh[10]
Cadaveric fascia lata[14] and acellular dermis,[7] NOS	Enduragen[18]	Bovine pericardium collagen, NOS[7,10,13,14]
Human biological mesh, NOS[21]	XenMatrix[10]	
	Small intestinal submucosa, NOS[7,14]	

NOS = not otherwise specified

Several SRs assessed non-comparative evidence.[9-12,15,22] Of the studies that did assess comparative evidence, comparators included:

- No mesh[2,13,14,16,19,20,24] or placebo[17]
- Synthetic mesh[8] or alternate mesh of any type[13]
- Alternate surgical approach[13,14]
- Muscle or tissue flap[16,21,25]
- Suture repair[7]

- Mechanical device[13]
- No treatment or conservative management[13]

The four evidence-based guidelines addressed multiple interventions, but the interventions relevant to this report included the use of biological meshes for abdominal wall hernia repair,[26] vaginal wall prolapse repair,[1] treatment of urinary incontinence,[27] and treatment of osteoarthritis of the shoulder joint.[28]

Outcomes

The main outcomes reported in the SRs included:

- Recurrence of hernia or prolapse[7-13,15]
- Wound or other surgical complications[8-15,18,20-22]
- Successful repair rate or failure rates[14,18]
- Erosion mesh[14,23]
- Patient symptoms[13,14,22]
- Patient satisfaction and quality of life[13,21,22]
- Length of hospital stay[20,21]

The main cost-effectiveness outcome reported by the three cost-utility analyses was the incremental cost-utility ratio (ICUR) for the evaluated biological mesh.[2,24,25]

Two guidelines[1,26] did not specifically state the outcomes considered. The NICE guideline[27] included the following outcomes for women with urinary incontinence: continence status, symptom reduction, adverse events, quality of life, psychological outcomes, and clinical measures. The guideline produced by the AAOS[28] included the following outcomes: patient-oriented outcomes (e.g., pain, quality of life) and outcomes for which there were data on at least 50% of patients.

Summary of Critical Appraisal

Additional details regarding the critical appraisal of included publications are provided in Appendix 3.

Systematic Reviews

The quality of the SRs included in this review was variable. The main critical appraisal points are as follows:

- With the exception of three reviews,[7,13,16] published protocols were not referred to; therefore, whether the review methodology was established a priori was usually unclear.
- Duplicate study selection was completed by many reviews[7,9,10,12-14,16,17,20,22] but it was not explicitly stated whether this was performed in others despite multiple authors listed.[8,11,15,18,19,21,23]
- The number of reviewers involved in extraction was unclear in several cases[8,9,11,12,14,18] and involved at least two reviewers at some stage of the process in others.[7,10,13,16,17,21,22]
- A comprehensive literature search including at least two databases was conducted for some,[8,10,11,13-16,21] but not all reviews.[7,9,12,18-20,22,23]

- For most reviews, the performance of a grey literature search was either unclear or lacking.[7-9,12,14,14,15,17-20,22,23]
- A list of included studies and study characteristics was provided by the majority of reviews, but was absent from or incomplete in some reviews.[15,18,22,23]
- One review had an unclear number of included studies.[21]
- One review did not adhere to its stated protocol by including an animal study that did not meet inclusion criteria.[9]
- Three reviews provided information regarding excluded studies.[10,13,17]
- One review had a discrepancy between the number of included studies reported in the text and meta-analysis figure.[23]
- The scientific quality of included studies was assessed by most reviews and at least mentioned in the discussion and conclusions.[7-11,13,16-18,20,21]
- The scientific quality of the included studies was not assessed, documented, and/or specifically addressed in the formulation of conclusions in five reviews.[14,15,19,22,23]
- Two reviews made conclusions about the comparative effectiveness of biological mesh versus synthetic mesh that were not supported by the analyses conducted.[14,23]
- For most studies that reported pooled results, statistical heterogeneity was assessed using the I^2 statistic.[7,8,11,13,14,16,17] There was substantial heterogeneity for certain outcomes (recurrence,[8,11] total wound complication rates,[8] objective failure rate compared with native tissue repair,[13] intraoperative blood loss,[14] subjective incidence of Frey's syndrome[17]) in some reviews that suggests that pooling was potentially inappropriate.
- One review did describe the methods used to pool results and heterogeneity was not assessed.[21]
- Publication bias was assessed by the minority of reviews[8,14,16,17,20] though the number of included studies was reported as a barrier to assessing publication bias in some cases.
- Several review authors declared no conflict of interest[7,8,10,11,19] or provided a conflict of interest or funding statement,[12,13,15,17,18,21-23] but in some cases it was unclear.[9,14,16,20]

The three economic evaluations[2,24,25] were conducted using similar study designs (all cost-utility analyses), data collection, and methods of analysis and interpretation of results. All had clear and appropriate research questions, viewpoints of the analyses, comparators, outcomes, and choice of economic evaluation. Need for procedure revision (probabilities of hernia recurrence or breast implant loss) and complication rates were based on literature searches. Relevant costs and their sources were described. The results of primary and sensitivity analyses were clearly presented; however, there were some model assumptions that may impact the validity of the conclusions drawn from these analyses. The main limitation of all three cost-utility analyses was the inappropriate use of utilities collected from surveyed surgeons. As values are assigned to a patient's health state, typical practice involves collecting utilities from patients or a healthy population; using utilities derived from surgeons' perspectives may inaccurately represent patients' quality of life and health preferences, thereby potentially skewing the results. The hernia repair economic evaluation also assumed that there was little variability in the selection and performance of surgical techniques; however, the authors acknowledged that this level of detail was generally not provided in the included studies, so this may not have been a valid assumption and increases uncertainty in the results.[2] In addition, all three economic evaluations lacked a clearly defined model time horizon and discount rates for costs and quality-adjusted life years (QALYs), which makes the time frame over which the analyses apply and the reliability of results unclear.

The methodological rigour of the four evidence-based guidelines[1,26-28] was variable; the NICE and AAOS guidelines were of high quality.[27,28] All guidelines had clearly stated objectives. Two were based on SRs of the available evidence;[26,28] however, few details regarding the conduct of the SR supporting the International Endohernia Society recommendations were provided, so the methodological quality of this review is unclear.[26] The NICE guideline did not include a systematic grey literature search but the literature search was otherwise thorough.[27] The guideline by Maher lacked detailed methodology for the literature search,[1] precluding the reader from assessing whether all relevant literature was captured to support the recommendations. The NICE[27] and AAOS[28] guidelines had clear patient populations, but this was not explicitly defined for the guidelines by the International Endohernia Society[26] and Maher.[1] Furthermore, it was unclear whether all relevant professional groups were included in the development of these two guidelines, which may limit their applicability to a wider clinical audience.[1,26] Patient or public input was sought in the development of two guidelines,[27,28] but not for the other two guidelines.[1,26] All guidelines used a grading system to evaluate the quality of the evidence upon which the recommendations were based, and there were explicit links between the evidence and specific recommendations in two guidelines.[27,28] Recommendations were clearly presented in all guidelines; however, they generally lacked detailed considerations of guideline implementation.

Summary of Findings

Detailed summaries of study findings and guidelines are provided in Appendix 4.

What is the clinical effectiveness of biological mesh products?

Seventeen SRs reported on the clinical effectiveness of biological mesh products.[7-23] In general, the evidence regarding the clinical effectiveness of biological mesh was positive or neutral (i.e., no statistically significant difference between biological mesh and another intervention). Wound or surgical site infections were the most commonly reported surgical complications, and major risks were rare. The evidence comparing biological mesh products with each other or with synthetic meshes was inconclusive. The majority of SRs concluded that there is a paucity of high quality evidence regarding the use of biological meshes for various surgical indications, and additional RCTs are required to elucidate their optimal place in clinical practice.[9-14,16-22] A list of key findings is summarized below. Additional details are provided in Table A7 (Appendix 4).

<u>Recurrence</u>

Reduced short-term recurrence rates[7] and recurrence with unspecified follow-up[13] with biological mesh were reported in two SRs, while no difference in long-term recurrence rates[7] and recurrence with unspecified follow-up[8,15] with the use of biological mesh was reported in three SRs. One SR[9] reported “acceptable” recurrence rates with biological mesh.

<u>Infections and Other Complications</u>

Reduced infectious wound complications were reported in one SR.[8] No difference in infection and other complication rates with the use of biological mesh was reported in seven SRs.[8,14,15,17,20,21,23] One SR[9] reported “acceptable” infection rates with biological mesh, while infections were “frequently reported” in one SR.[12]

Other Outcomes

- Insufficient evidence of improved patient satisfaction or quality of life was reported in one SR[13]
- Improved surgical success rates with biological mesh were reported in one SR[14]
- No evidence of additionally improved overall outcomes with biological mesh was reported in one SR[13]
- No additional improvement in perioperative outcomes with biological mesh was reported in one SR[14]
- Length of hospital stay: one SR[20] reported a length of stay of one to two days; one SR[21] reported shorter stays with biological mesh than with tissue flap repair
- Successful prevention of Frey's syndrome after parotidectomy was reported in two SRs[16,17]
- Successful wound healing with biological mesh use was reported in one SR[19]
- Successful breast reconstruction with biological mesh was reported in one SR[20]
- Successful perineal reconstruction with biological mesh was reported in one SR[21]

Biological Mesh versus Other Biological Meshes or Synthetic Mesh

One SR reported no significant difference in hernia recurrence rates between human and porcine biological meshes.[8] Another SR about hernia repair concluded that there was no evidence to recommend one type of biological mesh over another or over synthetic mesh.[10]

One SR[14] reported that biological mesh was more effective than synthetic mesh for vaginal prolapse repair, while no difference in clinical effectiveness between biological mesh and synthetic mesh for vaginal prolapse repair[23] and laparoscopic ventral mesh rectopexy[15] was reported in two SRs.

What is the cost-effectiveness of biological mesh products?

Three cost-utility analyses were identified that evaluated the cost-effectiveness from a third-party payer perspective of biological mesh for ventral hernia repair[2] or post-mastectomy breast reconstruction.[24,25] All three analyses used a willingness-to-pay threshold of USD $50,000/QALY to establish cost-effectiveness. When compared with surgery performed without biological mesh, the base case analyses demonstrated that biological mesh was cost-effective for ventral hernia repair with component separation (ICUR = USD $15,003/QALY) and for implant-based breast reconstruction (ICUR = USD $264/QALY). These results were robust to changes in complication rates and utilities, as well as the use of biological mesh retail costs in the breast reconstruction model,[24] but were sensitive to changes in recurrence rates in the hernia repair model; biological mesh with component separation would not be cost-effective at a hernia recurrence rate of lower than 16%.[2] Medicare reimbursement costs (USD $268.22 for biological mesh of any size) were used in the analysis, and it was noted that biological mesh would not be cost-effective at retail costs ($32.38/$cm^2$) for the average hernia defect size (230 cm^2), with an ICUR of USD $187,069/QALY.[2] Biological mesh was not cost-effective for single-stage breast reconstruction when compared with autologous dermal flap reconstruction (ICUR = USD $261,720/QALY).[25] Biological mesh would only become cost-effective if the complication rate with autologous dermal flap exceeded 20%.[25]

Additional details are provided in Table A8 (Appendix 4).

What are the evidence-based guidelines regarding appropriate clinical indications for biological mesh products?

Four evidence-based guidelines were identified that addressed the use of biological mesh products for the following indications: vaginal prolapse,[1] abdominal hernia,[26] surgical interventions for urinary incontinence,[27] and surgical interventions for osteoarthritis of the glenohumeral joint.[28] There were recommendations for the use of biological mesh in certain clinical situations for hernia repair and the treatment of urinary incontinence.[26,27] Conflicting evidence or a lack of evidence precluded the provision of conclusive recommendations regarding the use of biological mesh for vaginal prolapse and arthroscopic treatment of glenohumeral joint osteoarthritis.[1,28]

Two guidelines with unclear methodology regarding the use of biological mesh in breast reconstruction and emergency repair of complicated abdominal wall hernias are provided in Appendix 6.

What are the evidence-based guidelines regarding the use of biological mesh products?

Recommendations for the use of biological mesh products varied by indication and type of mesh. The following briefly describes the recommendations outlined in the identified evidence-based guidelines. Additional details are provided in Table A9 (Appendix 4).

The guideline from the International Endohernia Society recommended that cross-linked biological meshes may be used for laparoscopic repair of incisional and ventral hernias; however, it stated that non–cross-linked biological meshes with a bridging technique should not be used for this indication. The use of any biological meshes in a contaminated surgical field was cautioned.[26]

The guideline by Maher regarding anterior vaginal compartment surgery concluded that biological mesh was associated with better anatomical outcomes (but not subjective outcomes) than native tissue repair. However, polypropylene mesh was supported over biological mesh. There was conflicting and limited evidence about the use of porcine dermis and small intestine submucosa as graft materials.[1]

The NICE guideline recommended the use of autologous rectus fascial slings, synthetic mid-urethral tape, or open colposuspension for the management of stress urinary incontinence. Specifically regarding the use of biological slings for this indication, NICE recommends against offering anterior colporrhaphy, needle suspensions, paravaginal defect repair and the Marshall–Marchetti–Krantz procedure.[27]

Due to insufficient evidence, the AAOS could not make recommendations regarding the use of arthroscopic treatments (including biological grafts) or biologic interposition arthroplasty (including osteoarticular allograft, autograft, and interpositional soft tissue allograft) for the treatment of glenohumeral joint osteoarthritis.[28]

Limitations

The major limitation that affected and was reported by the majority of SRs, economic evaluations and guidelines was the paucity of high quality evidence available to inform the reviews, economic models, and recommendations. Comparative evidence from rigorously designed clinical trials for the relevant indications was rare at the time of the literature search and study selection by the authors of the SRs, so non-comparative evidence was included in several SRs.[9-12,15,18-20,22,23] Non-comparative studies lacking a control group are unable to account for the influence of confounding variables, which reduces confidence in the conclusions. Some SRs[14,23] inappropriately made comparisons between different non-comparative studies with unknown differences in study design and patient population to assess the effectiveness of biological mesh versus alternate interventions; this further weakens the validity of conclusions in those reviews. Length of study follow-up and methods of measuring outcomes were often unclear or variable, which may have resulted in differential outcome reporting between studies included in the same SR, and therefore draws into question the appropriateness of pooling results.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This report identified clinical and cost-effectiveness evidence regarding the use of biological mesh products for hernia repair or abdominal wall reconstruction, pelvic organ prolapse, head and neck reconstruction, extremity wound healing, perineal repair, and breast reconstruction. Several types of biological meshes derived from human, porcine, and bovine sources were assessed in the identified SRs. Most SRs contained low-quality evidence. In general, positive or neutral clinical outcomes were reported with the use of biological mesh products. There is some evidence to suggest that biological meshes are cost-effective compared with hernia repair or breast reconstruction performed without biological mesh products. However, the majority of included clinical and cost studies identified a need for further prospective, controlled trials to support the use of biological mesh products. Furthermore, the superiority of one type of biological mesh over another (biological or synthetic) remains unclear. Biological mesh may be considered in some circumstances for laparoscopic repair of incisional and ventral hernias, but due to the lack of high quality available evidence, few recommendations were made for the use of biological mesh within the identified guidelines.

These findings and conclusions are consistent with the previous CADTH review on the clinical and cost-effectiveness of biological mesh.[3] The previous report identified relevant publications for several surgical procedures: breast reconstruction, pelvic organ prolapse, mucogingival surgery, inguinal hernia repair, urethroplasty, treatment of diabetic foot ulcers, and decompressive hemicraniectomy. However, as there was a variety of clinical indications and types of biological mesh identified with few associated studies each, the results were interpreted with caution. In addition, no cost-effectiveness studies and one evidence-based guideline were identified for that review. Therefore, the initial CADTH review concluded that there was insufficient clinical and economic evidence to definitively establish appropriate uses for biological mesh products.[3]

Based on the publications identified for the current report, there remains a lack of sufficient evidence to guide clinical practice regarding the use of biological mesh products. RCTs that were not captured by the SRs included in this report because they were published after the SRs or did not meet SR inclusion criteria are provided in Appendix 6. Several surgical indications are addressed by this collection of RCTs with relatively few studies per indication. Therefore, it is

not immediately apparent whether this represents a significant amount of research on the clinical effectiveness of any particular mesh product or for any specific patient population that would support clinical decision making. Further rigorously designed RCTs are required to clarify comparative clinical effectiveness and safety of the many available biological mesh products for most surgical indications in which their use has been suggested.

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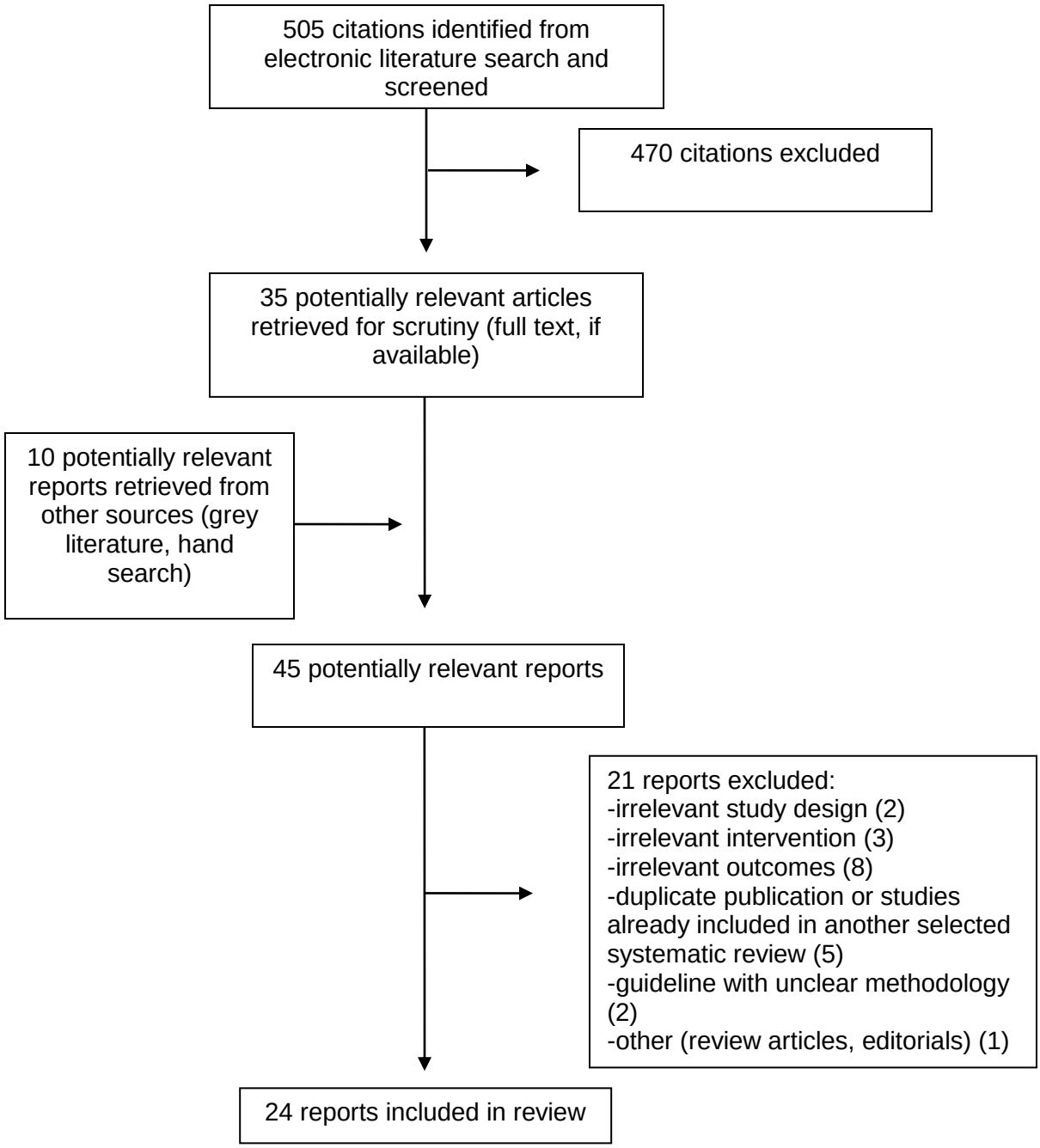
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention; Type(s) or Brand(s) of Biological Mesh	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Abdominal Wall Reconstruction and Hernia Repair					
Antoniou 2015, Germany[7]	Total: n = 5 RCTs, n = 2; prospective case-control study, n = 1; retrospective case-control studies, n = 2	Patients of any age undergoing hiatal hernia surgery	Biological mesh augmentation of hiatus; Human acellular cadaveric dermis, or porcine small intestine submucosa	Suture repair of hiatus	Hernia recurrence (measuring 2 cm or more) Follow-up for recurrence: short-term (6 to 12 months), medium-term (12 months to 3 years), Long-term (> 3 years)
Darehzereshki 2014, USA[8]	Retrospective studies, n = 8	Patients undergoing ventral hernia repair, n = 889	Biologic grafts (mesh); Alloderm, Strattice, Surgisis, Permacol	Non-biologic grafts (mesh)	Hernia recurrence rate, wound complication (infectious and noninfectious) Follow-up ranging from 7 to 66 weeks
Cross 2014, USA[9]	Non-comparative studies, n = 14	Patients undergoing abdominal wall reconstruction, n = 554	Biological mesh; Alloderm, Surgisis, Permacol, Collamend, Veritas, and Strattice)	No comparator	Infection and recurrence rates Follow-up: up to 6 months
Bellows 2013, USA[10]	Retrospective case series (56.7%), most with sample sizes < 30; cohort studies, case reports, descriptive case series; n = 60	Adult patients undergoing incisional/ventral hernia repair, n = 1212 total repairs	Biologic prosthesis; Human, porcine, bovine	No comparator	Recurrence, surgical site occurrence (complications) Follow-up duration ranged from 5 days to 60 months, overall mean of 13.6 months

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention; Type(s) or Brand(s) of Biological Mesh	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Slater 2013, Netherlands[11]	Retrospective studies, n = 26	Adult patients undergoing ventral hernia repair, n = 431 to 1152 depending on outcome	Biological grafts; Primarily Alloderm, Permacol and Surgisis	No comparator	Recurrence and complications Mean follow-up 18 months
Janis 2012, USA[12]	Total: n = 40 Retrospective studies, n = 37; prospective studies, n = 3	Patients undergoing abdominal wall reconstruction (including tumor resection, ventral and incisional hernias, acute trauma, intra-abdominal sepsis, and necrotizing fasciitis)	ADM AlloDerm, Permacol, SurgiMend	No comparator	Recurrence rates, complications (wound healing, infections, removal of mesh, seroma) Follow-up ranged from 0 to 74 months
Pelvic Organ Prolapse					
Maher 2013, Australia[13]	RCTs, total: n = 56 RCTs that evaluate biological mesh: biological graft vs. no mesh or native tissue, n = 7; biological graft vs. alternate mesh, n = 3	Adult women seeking treatment for symptomatic pelvic organ prolapse	Surgical procedures for pelvic organ prolapse; Subgroup: surgeries using biological grafts (including Pelvicol, Tutoplast, bovine pericardium collagen)	No treatment, conservative management, mechanical device, alternate surgical approach Subgroup: no biological graft, alternate mesh	Patient symptoms, satisfaction, QoL, recurrence, surgical outcomes and complications Follow-up < 1 year in 9 trials, 1 to 5 years in 43 trials, > 5 years in 4 trials
Min 2013, China[14]	RCTs, n = 20 synthetic and biological meshes, n = 2; biological mesh alone, n = 5	Women undergoing anterior vaginal wall prolapse repair	Anterior vaginal wall prolapse repair with mesh or graft (including biological meshes); Pelvicol, small intestine submucosa, cadaveric fascia lata, bovine pericardium	Another surgical technique using mesh or graft, surgery without mesh	Failure rate, surgical outcomes and complications, patient symptoms, material erosion Follow-up ranging from 3 to 36 months

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention; Type(s) or Brand(s) of Biological Mesh**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
Smart 2013, UK[15]	Prospective observational studies, n = 13 biological mesh, n = 2	Adult patients undergoing laparoscopic ventral rectopexy for rectal prolapse; n = 99 for biological mesh studies	Laparoscopic ventral rectopexy with biological or synthetic mesh; Permacol	Not necessary for inclusion	Recurrence rates, complications Median follow-up for 2 biological mesh studies was 12 months
Abed 2011, USA[23]	Comparative studies and case series, n = 126 Biological mesh, n = 30	Patients undergoing vaginal prolapse repair	Vaginal prolapse repair using graft materials (including biological mesh); Type of biological mesh not specified	Not necessary for inclusion	Adverse events: graft erosion, wound granulation, dyspareunia Follow-up not specified
Head and Neck Reconstruction					
Li 2013, China[16]	RCTs, n = 14; ADM vs. no ADM, n = 9; ADM vs. muscle flap, n = 1	Patients who had undergone parotidectomy, n = 1098 total	Grafts used in parotid surgery, including subgroup analysis of ADM; Brand of ADM not specified	No biological graft, muscle flap	RR of Frey's syndrome Follow-up ranging from 3 to 60 months
Zeng 2012, China[17]	RCTs and quasi-randomized studies, n = 5	Adult patients who had undergone parotidectomy, n = 409	ADM; AlloDerm	Placebo	RR of Frey's syndrome, complications Follow-up ranging from 5 to 39 months
Shridharani 2012, USA[18]	Comparative and non-comparative studies, n = 30	Patients who had undergone head and neck reconstruction using ADM	ADM; AlloDerm, Enduragen, Zyplast, Renov	Not necessary for inclusion	Successful reconstruction, adverse events Follow-up not specified

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention; Type(s) or Brand(s) of Biological Mesh**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
Upper and Lower Extremity Wound Healing					
Iorio 2012, USA[19]	Case series (n = 10) and RCTs (n = 3)	Patients with non–burn related, traumatic, chronic extremity wounds, n = 432	ADM; GraftJacket, Integra	No comparator, no ADM (3 RCTs)	Complete wound healing, time to readiness for skin graft, matrix incorporation Follow-up ranging from 15 to 325 days
Breast Reconstruction					
Jansen 2011, Canada[20]	Retrospective and prospective case series, cohort studies; n = 14	Adult patients undergoing post-mastectomy breast reconstruction	ADM; Alloderm	No comparator, no Alloderm (1 study)	Acute and long-term complications, length of hospital stay, aesthetics, volume and times for expansions Mean follow-up ranging from 8 to 56 months
Perineal Reconstruction					
Foster 2012, UK[21]	Prospective and retrospective observational studies; n = 11 or 12 Biological mesh, n = 5; Tissue flap, n = 6 or 7	Patients undergoing perineal reconstruction following ELAPE for rectal cancer, n = 85 for biological mesh studies	Biological mesh; Permacol, human ADM, Surgisis	Myocutaneous flap, fasciocutaneous flap	Mortality, complications, perineal hernia, chronic pain, QoL, length of hospital stay Follow-up ranging from 8 to 20 months (biological mesh studies) and 10 to 38 months (tissue flap studies)

Table A1: Characteristics of Included Systematic Reviews and Meta-Analyses					
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics**	**Intervention; Type(s) or Brand(s) of Biological Mesh**	**Comparator(s)**	**Clinical Outcomes, Length of Follow-Up**
Multiple Indications					
Jansen 2013, Canada[22]	Total: n = 311; Basic science (n = 86), RCTs, cohort, case control, case series, case reports or expert opinion Anatomical areas: head and neck, n = 82; trunk, n = 66; breast, n = 34; skin, n = 25; pelvis, n = 10; extremities, n = 8	For clinical studies: patients who have had a procedure involving AlloDerm; Anatomical areas of application include: breast, skin, extremities, head and neck, trunk, pelvis	ADM; AlloDerm	Not necessary for inclusion	Any, including: complications (e.g., infections, seroma), healing, pain, patient symptoms and satisfaction Follow-up not specified

ADM = acellular dermal matrix; ELAPE = extralevator abdominoperineal excision; QoL = quality of life; RCT = randomized controlled trial; RR = relative risk; UK = United Kingdom; USA = United States of America

Table A2: Characteristics of Included Economic Evaluations

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Chatterjee 2015, USA[2]	Cost-utility analysis Third party payer (government) and hospital/physician	Biologic mesh (Strattice) vs. no biologic mesh	Patients with complex ventral hernias requiring repair with component separation	Lifetime	• Average patient age of 50 years • Little variability in clinical judgement and surgical technique • Treatment and/or recovery from early complications within 30 days • Long-term complications only in patients without early complications, admission after 30 days, recovery within 3 months • Permanent mesh not an option • Maximum of two hernia recurrences; successful revision assumed after second recurrence repair
Krishnan 2014, USA[24]	Cost-utility analysis Third party payer (government) and hospital/physician	ADM (AlloDerm) vs. no ADM	Patients receiving two-stage, expander–implant immediate breast reconstruction following mastectomy	Lifetime	• Average patient age of 45 years, life expectancy 81.1 years • 6 month recovery for mastectomy flap necrosis • 1 month recovery for: major and minor infection, explantation, hematoma, seroma, capsular contracture
Krishnan 2013, USA[25]	Cost-utility analysis Third party payer (government)	ADM (AlloDerm) vs. autologous dermal flaps	Patients receiving one-stage, implant-based immediate breast reconstruction following mastectomy	Lifetime	• Average patient age of 45 years, life expectancy 81.1 years • 6 month recovery for mastectomy flap necrosis • 1 month recovery for: major and minor infection, explantation, hematoma, seroma, capsular contracture

ADM = acellular dermal matrix; USA = United States of America; vs. = versus.

Table A3: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
Bittner 2014[26,29] – International Endohernia Society						
Intended users: surgeons Target population: patients with abdominal wall hernias	Laparoscopic treatment of ventral and incisional abdominal wall hernias	Not stated	Systematic review	Levels of evidence (1A to 5) and strength of recommendations (A to D) rated according to provided scheme	Consensus conference to review the drafts resulting from the literature reviews	Expert review of draft guidelines
Maher 2013[1] – Committee on Pelvic Organ Prolapse Surgery						
Intended users: surgeons Target population: patients with pelvic organ prolapse	Anterior vaginal compartment pelvic organ prolapse surgery	Success rate, complications	Literature review	Levels of evidence (1 to 4) and strength of recommendations (Grade A to D) rated according to provided scheme	Committee based recommendations based on the review of the literature, with consideration to the strength and quality of the recommendation	Not stated
NICE 2013[27] – National Collaborating Centre for Women's and Children's Health						
Intended users: care providers for women with urinary incontinence Target population: women with urinary incontinence	Diagnosis and management of urinary incontinence in women	Continence status, symptom reduction, adverse events, quality of life, psychological outcomes, and clinical measures	Systematic review	Levels of evidence (1++ to 4) and quality of evidence was assessed using GRADE	Informal consensus for draft recommendations, with formal consensus (voting) from the guideline development group for final recommendations	Peer review, and external review from registered stakeholder organizations

Table A3: Characteristics of Included Guidelines

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
American Academy of Orthopaedic Surgeons 2009[28]						
Intended users: primary users - surgeons, physicians, health care professionals managing treatment of osteoarthritis of the glenohumeral joint; secondary users - decision makers and developers of guidelines Target population: adults (aged 19 years or older) with diagnosed osteoarthritis of the glenohumeral joint	Treatments for osteoarthritis of the glenohumeral joint	Patient-oriented outcomes; outcomes for which there was data on ≥50% of patients	Systematic review	Levels of evidence (I-V) and strength of recommendations (strong, moderate, limited, inconclusive, consensus) (pages 6-8)	Work group development of recommendations based on GRADE	External peer-review and public commentary

CADTH = Canadian Agency for Drugs and Technologies in Health

APPENDIX 3: Critical Appraisal of Included Publications

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[4]

Author	Strengths	Limitations
Abdominal Wall Reconstruction and Hernia Repair		
Antoniou 2015[7]	• Protocol published prior to conduct of study • Search not restricted by language or date • Study selection performed by two independent reviewers • Data extracted by one author and checked by a second • List of included studies provided along with study characteristics • Scientific quality of studies assessed using the Cochrane Risk of Bias tool • Scientific quality considered in formulation of conclusions • Statistical heterogeneity assessed using I^2 statistic • No conflict of interest declared by the review authors	• Single database searched • No grey literature search disclosed • Restriction by language or publication type unclear • List of excluded studies not disclosed • Some studies included in meta-analysis reported to have conflict of interest • Small number of studies pooled did not allow for assessment of publication bias
Darehzereshki 2014[8]	• List of included studies provided along with study characteristics • Multiple databases searched • Statistical heterogeneity assessed using I^2 statistic • Quality of studies assessed descriptively based on methodological strength and strength of reporting (no checklist used) • Scientific quality considered in formulation of conclusions • Publication bias analyzed using funnel plots • No conflict of interest declared by the review authors	• No evidence of a priori design • List of excluded studies not provided • No formal grey literature search conducted (but reference lists searched) • Number of reviewers involved in study selection and data extraction unclear (mention that discrepancies resolved by consensus)
Cross 2014[9]	• Study selection performed by three independent reviewers • List of included studies and study characteristics provided • Scientific quality of studies assessed by three reviewers using the US Agency for Healthcare Research and Quality standardized scoring system, and Methodological Index for Non-Randomized Studies	• No evidence of a priori design • Number of reviewers involved in data extraction unclear • Single database searched • No grey literature search disclosed • Minimal study characteristics presented for included studies • Name of first author and publication year not reported in

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[4]		
Author	**Strengths**	**Limitations**
	analysis • Scientific quality considered in formulation of conclusions	text • Direct link of included studies to references unclear • List of excluded studies not disclosed • No formal meta-analytic methods performed (pooled rates) • Heterogeneity among interventions (different types of mesh and abdominal reconstruction procedures) • Conflict of interest and financial support unclear • Number of studies reported incorrectly • Both human and animal studies included despite exclusion of animal studies stated in methods • Information in study characteristics table does not match cited references • Many included studies did not differentiate between superficial and deep infections • Most included studies used poor methodology • No comparative data; therefore equivalency or superiority to synthetic products could not be established
Bellows 2013[10]	• Study selection and data extraction performed by two independent reviewers (third if disagreement) • List of included studies provided along with study characteristics, supplementary files provided regarding excluded studies • Three electronic databases searched • Study quality assessed based on strength of evidence and methodological quality by two authors with disagreements resolved by third reviewer • Rate and effect estimates recalculated where authors did not consider drop-outs and loss to follow up • Wound classification system established using the Ventral Hernia Working Group grading system based on patient information or consultation with study authors • Due to clinical and methodological heterogeneity, no pooling of studies was performed	• No evidence of a priori design • No formal grey literature search disclosed beyond hand searching of reference lists • Studies of very low methodological quality (e.g., retrospective studies, case reports, case series, commentaries, letters to the editor, expert opinions) • High risk of selection and information bias, generally poor methodologic quality, missing or incomplete data • No comparative data; therefore equivalency or superiority to synthetic products could not be established

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[4]		
Author	**Strengths**	**Limitations**
	• No conflict of interest or financial conflicts reported by authors • List of ongoing trials with potential relevant data (i.e., for updates) included • Ventral Hernia Working Group grading of hernia class performed	
Slater 2013[11]	• Multiple electronic databases searched • No restriction by publication type • Grey literature search completed • List of included studies and study characteristics provided • Scientific quality of studies assessed independently by two authors using a modified version of the methodological index for nonrandomized studies tool • Quality of studies considered in formulation of conclusions • Heterogeneity assessed using the I^2 statistic • No conflict of interest declared	• No evidence of a priori design • Number of reviewers involved in study selection and data extraction unclear • List of excluded studies not provided • At time of publication no RCTs comparing biological and synthetic • Publication bias not assessed • No comparative data; therefore equivalency or superiority to synthetic products could not be established
Janis 2012[12]	• No search restriction by publication type evident • Study selection performed by two independent reviewers • Reference lists searched for additional articles • List of included studies provided • Evidence-rating mentioned in formulation of conclusions • No financial conflict of interest reported	• No evidence of a priori design • Number of reviewers involved in extraction, unclear • Single database searched • No grey literature search disclosed • No list of excluded studies provided • No formal quality assessment completed • Quality of studies mentioned briefly in discussion • Heterogeneity among patient populations prevented pooling of results, results only described narratively so overall effects unclear • Risk of publication bias not assessed • Substantial industry affiliations of authors reported • Intervention of some included studies included both biological and synthetic mesh (combined intervention)

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[4]		
Author	**Strengths**	**Limitations**
Pelvic Organ Prolapse		
Maher 2013[13]	• A priori design provided • Study selection and data extraction performed in duplicate • Comprehensive literature search was performed • Grey literature searched and included • List of included and excluded studies provided • Characteristics of included studies provided • Scientific quality of each included study was assessed, documented, and used to formulate conclusions • Appropriate methods used to combine study findings • Conflict of interest potential assessed for each study and funding sources for the review declared	• Likelihood of publication bias not addressed
Min 2013[14]	• Study selection performed in duplicate with consensus procedure • Comprehensive literature search was performed • List of included studies and their characteristics included • Appropriate methods used to combine study findings • Likelihood of publication bias assessed	• No a priori design provided • Unclear whether data extraction was performed in duplicate • Unclear whether publication status was used as an inclusion criterion • List of excluded studies not provided • Scientific quality of studies assessed but not presented individually for each study • Scientific quality of studies not used appropriately in formulating conclusions • Conclusions were extrapolated from comparisons that were not directly tested (biological mesh vs. synthetic mesh) • Conflict of interest not provided for each individual study
Smart 2013[15]	• Comprehensive literature search was performed • List of included studies provided • Conflict of interest declaration provided for review	• No a priori design provided • Unclear whether study selection was performed in duplicate with a consensus procedure for disagreements • Unclear whether grey literature was searched • List of excluded studies not provided • Incomplete list of study characteristics (no patient demographics)

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[4]		
Author	**Strengths**	**Limitations**
		• Scientific quality of the included studies not documented or used to formulate conclusions • Likelihood of publication bias and conflict of interest for included studies not addressed
Abed 2011[23]	• Conflict of interest declaration for review authors provided	• No a priori design provided • Unclear whether study selection was performed in duplicate, data extraction performed by a single investigator • Single database searched • Unclear whether grey literature was searched • List of included and excluded studies not provided • Characteristics of included studies not provided • Discrepancy between number of included studies reported in text and meta-analysis figure • Scientific quality of the included studies not assessed, documented, or used to formulate conclusions • Conclusions were extrapolated from comparisons that were not directly tested (biological mesh vs. synthetic mesh) • Tests for heterogeneity not reported • Likelihood of publication bias or conflict of interest of included studies not addressed
Head and Neck Reconstruction		
Li 2013[16]	• A priori design provided (protocol developed in advance, ethics approval obtained) • Study selection, data extraction, and assessment of evidence quality performed in duplicate • Comprehensive literature search was performed • Publication status used as inclusion criterion • List of studies with relevant characteristics provided • Scientific quality of each included study was assessed, documented, and used to formulate conclusions • Appropriate methods used to combine study findings • Likelihood of publication bias addressed	• List of excluded studies not provided • Conflict of interest declarations not provided

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[4]		
Author	**Strengths**	**Limitations**
Zeng 2012[17]	• Study selection, data extraction, and assessment of evidence quality performed in duplicate • Comprehensive literature search was performed • List of included and excluded studies provided • Characteristics of included studies provided • Scientific quality of included studies assessed, documented, and used to formulate conclusions • Appropriate methods used to combine study findings • Potential for publication bias and conflict of interest addressed	• No published, a priori design provided • Publication status not used as inclusion criterion
Shridharani 2012[18]	• List of included studies provided • Scientific quality of included studies assessed, documented, and used to formulate conclusions • Conflict of interest declaration provided	• No published, a priori design provided • Unclear whether study selection occurred in duplicate • Single database used for literature search • No mention of additional grey literature search • Only published articles included in review • List of excluded studies not provided • Incomplete summary of included study characteristics • No discussion of publication bias
Upper and Lower Extremity Wound Healing		
Iorio 2012[19]	• List and characteristics of included studies provided • Scientific quality of the included studies was assessed and documented • Authors disclosed absence of financial interests or external support	• A priori design not provided • Unclear whether study selection and data extraction occurred in duplicate • Unclear whether electronic database search was supplemented • Unclear whether grey literature was included in the search • List of excluded studies not provided • Quality of the evidence not explicitly addressed for formulation of conclusions • No assessment of likelihood of publication bias or conflict of interest for included studies

Table A4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[4]		
Author	**Strengths**	**Limitations**
Breast Reconstruction		
Jansen 2011[20]	• Study selection and data extraction performed in duplicate • List and characteristics of included studies provided • Scientific quality of the included studies was assessed and documented • Likelihood of publication bias addressed	• A priori design not provided • Multiple electronic databases searched but literature not supplemented with search in other sources • Unclear whether grey or unpublished literature was searched • List of excluded studies not provided • Source of funding or support for included studies not provided
Perineal Reconstruction		
Foster 2012[21]	• Comprehensive literature search was performed with supplemental sources to multiple electronic databases • List and characteristics of included studies provided • Scientific quality of included studies was assessed and documented • Scientific quality explicitly addressed and used to formulate conclusions • Conflict of interest declarations for review authors provided	• A priori design not provided • Data extracted by two independent reviewers; however, unclear whether study selection was performed in duplicate or if a consensus procedure was in place • Unclear whether status of publication was used as an inclusion criterion • Unclear number of studies included in primary analysis • List of excluded studies not provided • No description of methods to pool data provided, heterogeneity not assessed • Likelihood of publication bias and conflict of interest for included studies not addressed
Multiple Indications		
Jansen 2013[22]	• Study selection and data extraction were performed in duplicate • Conflict of interest declarations for review authors provided	• A priori design not provided • Multiple electronic databases searched but literature not supplemented with search in other sources • Unclear whether status of publication was used as an inclusion criterion • Full list of included studies not provided, excluded studies list not provided • Characteristics of all included studies not provided • Level of evidence overall provided, but scientific quality of each article not assessed with a formal quality tool to be documented in the results and conclusions • Risk of publication bias mentioned but not explained • Conflict of interest not assessed for included studies

Table A5: Strengths and Limitations of Economic Studies using Drummond Checklist[5]	
Strengths	**Limitations**
Chatterjee 2015[2]	
• Clearly stated research questions, interventions and comparators, outcome measures, analysis perspective, rationale for and choice of economic evaluation • Sources and method of synthesis for probability estimates of complications clearly defined • Decision model and estimation of costs and QALYs clearly explained • Appropriate choice of sensitivity analyses • Main results clearly presented	• Analysis time horizon not clearly defined • Utilities collected from surgeons rather than a patient or healthy population • Discount rate not stated; no explanation provided • Limitations of literature but not of the economic analysis methods addressed in conclusions
Krishnan 2014[24]	
• Clearly stated research questions, interventions and comparators, outcome measures, analysis perspective, rationale for and choice of economic evaluation • Sources and method of synthesis for probability estimates of complications clearly defined • Decision model and estimation of costs and QALYs clearly explained • Appropriate choice of sensitivity analyses • Main results clearly presented	• Analysis time horizon not clearly defined • Utilities collected from surgeons rather than a patient or healthy population • Discount rate not stated; no explanation provided • Limitations of literature but not of the economic analysis methods addressed in conclusions
Krishnan 2013[25]	
• Clearly stated research questions, interventions and comparators, outcome measures, analysis perspective, rationale for and choice of economic evaluation • Sources and method of synthesis for probability estimates of complications clearly defined • Decision model and estimation of costs and QALYs clearly explained • Appropriate choice of sensitivity analyses • Main results and associated conclusions clearly presented	• Analysis time horizon not clearly defined • Utilities collected from surgeons rather than a patient or healthy population • Discount rate not stated; no explanation provided

Table A6: Strengths and Limitations of Guidelines using AGREE II[6]	
Strengths	**Limitations**
Bittner 2014 – International Endohernia Society[26,29]	
• A systematic search of the literature, including clearly stated search terms, was performed • Questions covered by the guideline and the recommendations were clearly stated and easily identifiable • The hierarchy used for grading the evidence, and the grading scale for the recommendations were stated in part 1 of the guideline • Views and opinions of clinical experts was sought	• Unclear whether the guideline development group was inclusive of all relevant professional groups, including nurses and general practitioners • Views and preferences of patients and the public were not included • Specific patient population not clearly described • No discussion of the guideline's implementation in clinical practice • A procedure for updating the guideline was not included • Unclear whether contributing authors had conflicts of interest
Maher 2013[1]	
• The objective is clearly stated • The hierarchy used for grading the evidence, and the grading scale for the conclusions were clearly stated	• Detailed literature search methodology is lacking • Unclear whether all relevant groups were included in the development of the report • Views and preferences of patients and the public were not included • Target users of the report are unclear, though it is implied it is surgeons treating pelvic organ prolapse • No explicit link between recommendations and key supporting evidence • No discussion of the guideline's implementation in clinical practice • A procedure for updating the guideline was not included • Unclear whether contributing authors had conflicts of interest
NICE 2013[27]	
• Guideline aims and questions are clearly stated • The guideline development group included patient/carer representative and members of the public • A systematic search of the published literature was used • The intended users of the guideline and target population are clearly stated • The evidence is clearly linked to the recommendations made • The methods for formulating the recommendations, and the recommendations are clearly stated • A procedure for updating the guideline is provided	• There was no systematic search of the grey literature • Barriers and facilitators to the clinical application of the guideline are not described

Table A6: Strengths and Limitations of Guidelines using AGREE II[6]	
Strengths	**Limitations**
AAOS 2009[28]	
• A systematic search of the literature was used • The intended users of the guideline and target population are clearly stated • Public commentary was sought on the draft guideline and recommendations • Regarding the recommendations, implications for clinical practice are clearly stated • A procedure for updating the guideline is provided • The link between evidence and the recommendations are clearly stated • Guideline includes dissemination plans for its findings	• Barriers and facilitators to the clinical application of the guideline are not described

AAOS = American Association of Orthopaedic Surgeons; NICE = National Institute for Health and Care Excellence

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A7: Summary of Findings of Included Systematic Reviews

Author	Main Study Findings	Author's Conclusions
Abdominal Wall Reconstruction and Hernia Repair		
Antoniou 2015[7]	Suture repair vs. biological mesh: • Short-term recurrence rate: 16.7% vs. 3.7% (5 studies; OR = 3.74, 95% CI 1.55 to 8.98, I^2 = 0%) • Long-term recurrence rate: 51.3% vs. 42.4% (1 study; OR = 1.43, 95% CI 0.56 to 3.63 • Medium-term recurrence rate: not reported	• Overall, biological mesh appears to be advantageous over suture repair in the short-term • Lower odds of short term recurrence observed for the biological mesh group • No difference in long-term recurrence rates • Subgroup analysis of studies with short term follow up showed no significant difference between groups (p = 0.07)
Darehzereshki 2014[8]	Biological mesh vs. no mesh (8 studies): • Rate of recurrence: 18.6% vs. 15.7% (OR = 0.7, 95% CI 0.21 to 2.76, *P* = 0.67, I^2 = 82%) • Infectious wound complication rates: 10.9% vs. 36.5% (OR = 0.18, 95% CI 0.09 to 0.37, *P* <0.00001, I^2 = 0%) • Non-infectious wound complication rates: 13.2% vs. 3.4% (OR = 1.33, 95% CI 0.03 to 50.75, *P* = 0.88, I^2 = 57%) • Total wound complication rate: OR = 0.35, 95% CI 0.09 to 1.40, *P* = 0.14, I^2 = 67%	• Biological mesh use resulted in reduced infectious wound complications and similar recurrence rates when compared with non-biological mesh • Subgroup analysis: hernia repairs with biologic mesh and CST trended (non-significant) towards higher recurrence than repairs with non-biologic and CST • Procedures without CST trended (non-significant) towards higher recurrence rate for non-biologic mesh versus biological mesh • No difference in recurrence rates for human versus porcine-derived mesh
Cross 2014[9]	• Overall recurrence rate: 109/554 (20%) • Rate of post-operative infection (deep or superficial): 135/554 (24%)	• There is a lack of evidence to support the use of biological mesh for contaminated hernia defects • Authors report that overall recurrence rate of 20 percent and infection rate of 24 percent were 'acceptable' • Individual rates of recurrence by type of mesh ranged from 9% to 64%; rates of infection ranged from 9% to 50% by type of mesh • Prospective studies regarding the use of biological mesh products in contaminated or infected fields are needed

Table A7: Summary of Findings of Included Systematic Reviews

Author	Main Study Findings	Author's Conclusions
Bellows 2013[10]	• Overall mortality rate: 48/1212 (4%) • Hernia recurrence (weighted rate): 15.2% • Overall surgical site occurrence: 491/930 (52.8%) • Post-operative infection: 157/930 (16.9%) • Seroma/hematoma: 112/930 (12%) • Mesh disintegration: 5/930 (0.6%) • Flap necrosis: 3/930 (0.3%) • Explantation of device: 19/930 (2%)	• Overall, there is a paucity of high-quality evidence on the use of biological tissue grafts for incisional hernia repair • Incidence of surgical site occurrence was lowest for xenogenic pericardium, and highest for porcine • No robust evidence to suggest that any biological prosthetic is superior over alternative biologic or synthetic prostheses • Lowest rates of short-term (< 2 years) recurrence seen with porcine small intestinal submucosa and highest in ADM
Slater 2013[11]	Recurrence rate: • Overall (in studies with ≥ 12 months of follow-up): 86/531 (17 studies; weighted pooled proportion 13.8% , 95% CI 7.6 to 21.3) • Clean/clean-contaminated wound class: 9/213 (5 studies; weighted pooled proportion 2.9%, 95% CI 0.2 to 8.3, I^2 = 68.4%) • Contaminated/dirty wound class: 22/84 (7 studies; weighted pooled proportion 23.1%, 95% CI 11.3 to 37.6, I^2 = 52.9%) • Complicated wound class: 55/234 (8 studies; weighed pooled proportion 19.4%, 95% CI 11.4 to 29.0, I^2 = 64.2%) Surgical morbidity and mortality rates: • Mortality: 36/879 (4.1%; reported in 19 studies) • Overall surgical morbidity: 584/1152 (25 studies; 46.3%, 95% CI 33.3 to 59.6) • Wound infections: 246/1109 (15.9%, 95% CI 9.8 to 23.2) • Removal of prosthesis: 12 patients (4.9%) • Seroma formation: 115/827 (14.2%, 95% CI 9.5 to 19.5%)	• Significantly less recurrence in the clean/clean-contaminated wound class versus contaminated/dirty and complicated groups; no differences between contaminated/dirty and complicated group; recurrence rate increased with level of contamination • Post-operative infection, total surgical morbidity significantly associated with hernia recurrence • Infection rate significantly higher in contaminated/dirty than clean/clean contaminated, complicated versus clean/clean contaminated • Surgical morbidity rate was higher in contaminated/dirty versus clean/clean contaminated and complicated versus clean/clean-contaminated • High complication and recurrence rates in contaminated and dirty fields, high salvage rate of prosthesis in cases of infection • Further research is needed to determine durability (long-term trials)
Janis 2012[12]	Hernia recurrence: • Incidence ranged from 0% to 80% among studies • One study reported a short-term (9 month) recurrence rate of 20% • Two studies reported a long-term recurrence rate of 80% (one at 24 months with the use of human matrix as an inter-	• Absence of high-quality evidence • Inconsistency in rates of recurrence • Recurrence rate increases over time • Infections were 'frequently reported' and ranged from superficial to deep wounds

Table A7: Summary of Findings of Included Systematic Reviews		
Author	**Main Study Findings**	**Author's Conclusions**
	positional graft, another with follow-up to 31 months) • Numerically lower rate of recurrence observed in patients who received human matrix versus synthetic mesh in two studies, whereas two studies observed an increased risk of recurrence with human matrix. Wound healing and infection: • Delayed wound healing: Occurred in up to 64% of patients • Infection rates not reported	
Pelvic Organ Prolapse		
Maher 2013[13]	No mesh vs. biological mesh for anterior or posterior prolapse repairs: • No significant difference in number of women with prolapse symptoms after colporrhaphy with and without biological mesh (3 studies; RR = 1.03, 95% CI 0.61 to 1.75, *P* = 0.90, I^2 = 0%) • No significant difference in objective failure rate at any site after native tissue repair (6 studies; RR = 1.35, 95% CI 0.74 to 2.46, *P* = 0.33, I^2 = 66%) No mesh vs. biological mesh for anterior prolapse repair: • Significantly fewer women with anterior prolapse/cystocele (objective failure) after anterior colporrhaphy with and without biological mesh (5 studies; RR = 1.56, 95% CI 1.13 to 2.14, *P* = 0.0064, I^2 = 0%) • Significantly lower objective recurrence rate on examination after anterior colporrhaphy with porcine dermal mesh (Pelvicol) than without (3 studies; RR = 1.57, 95% CI 1.05 to 2.35, *P* = 0.027, I^2 = 0%) Biological mesh vs. alternate mesh • 3 studies identified comparing Pelvicol with alternate meshes (Prolene Soft, Gynemesh, Vicryl); data not pooled • Pelvicol was associated with lower rates of objective recurrence in one study, similar prolapse symptoms in one study, and lower success rates in one study, when compared with alternate meshes	• Less recurrent anterior wall prolapse after repair supplemented with porcine dermal mesh inlay, but insufficient evidence to suggest improved patient satisfaction, quality of life, or reduced operations for recurrences with biological mesh • No evidence to suggest that addition of biological mesh for posterior vaginal compartment repair improved patient outcomes. • Insufficient data from RCTs to guide clinical practice

Table A7: Summary of Findings of Included Systematic Reviews		
Author	**Main Study Findings**	**Author's Conclusions**
Min 2013[14]	Biological mesh vs. no mesh for anterior prolapse repair: • Significantly lower anatomy failure rate with biological mesh (7 studies; RR = 0.60, 95% CI 0.45 to 0.82, *P* = 0.001, I^2 = 0%) • Significantly longer operative time with biological mesh (2 studies; MD = 14.90, 95% CI 6.03 to 23.76, *P* = 0.001, I^2 = 0%) • No significant difference between groups in intraoperative blood loss (2 studies; MD = 16.59, 95% CI –56.28 to 89.45, *P* = 0.66, I^2 = 79%) • No significant difference between groups in postoperative pain (1 study; RR = 0.25, 95% CI 0.06 to 1.11, *P* = 0.07) • No significant difference between groups in postoperative urinary tract infection rate (2 studies; RR = 0.67, 95% CI 0.09 to 4.79, *P* = 0.69, I^2 = 69%) • No significant difference between groups in de novo dyspareunia rate (2 studies; RR = 0.54, 95% CI 0.12 to 2.43, *P* = 0.42, I^2 = 0%) • Biological mesh erosion rate reported in 3 studies: cumulative rate 2/79 patients (2.53%)	• Anterior prolapse repair with adjuvant materials (including biological mesh) improves surgical success rates • Biological mesh was more effective than synthetic mesh • Biological mesh does not decrease operation time or improve blood loss, postoperative pain, postoperative urinary tract infection rate, or dyspareunia • Overall, adjuvant materials are safe and effective, though more high quality studies with long-term follow-up are required
Smart 2013[15]	• 2 studies evaluated biological mesh for laparoscopic ventral mesh rectopexy, porcine dermis (Permacol) in both; data were not pooled • Recurrence rate: 4/99 patients (4%) • No mesh-related complications or removal • No difference between studies of synthetic or biological mesh in recurrence rates (28/767 vs. 4/99, *P* = 0.78) or complication rates (5/767 vs. 0/99, *P* = 1.0)	*"Laparoscopic [ventral mesh rectopexy] for pelvic organ prolapse can be performed using a synthetic or biological mesh. The studies included in this review are heterogeneous and the complication rates may have been under-reported. From the available data, there is no difference in short-term recurrence or mesh complication rates between the two different types of mesh."* Pg. 653
Abed 2011[23]	• Graft erosion rate (biological mesh studies, n = 20): 85/1345, 10.1% (95% CI 8.3% to 12.3%) • Wound granulation rate(biological mesh studies, n = 7): 43/649, 9.1% (95% CI 6.8% to 12.1%) • Dyspareunia rate (biological mesh studies, n = 16): 66/1072, 9.6% (95% CI 7.6% to 12.1%) • No significant difference in AE rates between those reported in studies of biologic mesh and studies of synthetic mesh	• Granulation tissue formation was more commonly reported in biological mesh studies than synthetic mesh studies (not statistically significant) • Dyspareunia and graft erosion occurred at similar rates in studies of biological mesh and synthetic mesh. • RCTs are required to evaluate relative benefits and harms of different meshes, which subgroups of patients are likely to benefit from mesh use, and to establish risk factors for mesh-related AEs.

Table A7: Summary of Findings of Included Systematic Reviews		
Author	**Main Study Findings**	**Author's Conclusions**
Head and Neck Reconstruction		
Li 2013[16]	ADM vs. no ADM (9 studies): • By objective assessment with Minor's starch-iodine, ADM reduced risk of Frey's syndrome by 82% (RR = 0.18, 95% CI 0.12 to 0.26, *P* < 0.00001, I^2 = 0%) • By subjective assessment with no active treatment involved, ADM reduced risk of Frey's syndrome by 86% (RR = 0.14, 95% CI 0.07 to 0.28, *P* < 0.00001, I^2 = 0%) • AEs in 11 cases: 9 in ADM group (7 sialoceles), 2 in no ADM group • High GRADE quality of evidence ADM vs. SMAS folded flap (1 study): • No significant difference between groups (RR = 0.73, 95% CI 0.15 to 3.53, *P* = 0.70) • Low GRADE quality of evidence	*"In conclusion, the present clinical evidence suggests that grafts are effective in preventing Frey syndrome after parotidectomy. More RCTs are needed to confirm this conclusion and prove the safety of graft usage."* Pg. 426
Zeng 2012[17]	• Significantly lower objective incidence of Frey's syndrome with AlloDerm (4 studies; RR = 0.15, 95% CI = 0.08 to 0.30, *P* < 0.00001, I^2 = 0%) • Significantly lower subjective incidence of Frey's syndrome with AlloDerm (4 studies; RR = 0.16, 95% CI = 0.09 to 0.28, *P* < 0.00001, I^2 = 71%) • Two trials reported better facial contour and symmetry and finer scars with AlloDerm than without • No significant increase in wound infection and rejection with AlloDerm than without (4 studies; RR = 3.00, 95% CI = 0.14 to 65.90, *P* = 0.49) • No significant increase in seroma or sialocele with AlloDerm (3 studies; RR = 1.36, 95% CI = 0.66 to 2.80, *P* = 0.40, I^2 = 0%) • Significantly lower incidence of salivary fistula with AlloDerm (2 studies; RR = 0.09, 95% CI = 0.01 to 0.66, *P* = 0.02) • No significant difference in facial nerve paralysis with AlloDerm (3 studies; RR = 0.96, 95% CI = 0.84 to 1.09, *P* = 0.51)	*"In conclusion, evidence from the included studies suggests that use of AlloDerm results in decreased total incidence of Frey syndrome. Evidence also suggests that AlloDerm improves facial contour, may reduce salivary fistula and facial nerve paralysis, without adverse events. Yet limited data from the included studies is currently available to confirm this. Our study also shows that it is unclear whether the use of AlloDerm permits any conclusions about the incidence of other perioperative complications. Further studies are required to establish the optimal design and optimal outcome indicators."* Pg. 979

Table A7: Summary of Findings of Included Systematic Reviews		
Author	**Main Study Findings**	**Author's Conclusions**
Shridharani 2012[18]	• A narrative summary of studies (comparative and non-comparative) involving ADM for head and neck reconstruction was provided. Studies on Frey's syndrome addressed in this review but not discussed here as they are included in meta-analyses from other systematic reviews summarized in this report. Nose: • ADM successfully used for secondary rhinoplasty (short-term mild edema and seroma, long-term partial graft resorption in 45% of patients) and septal perforation repair (successful outcomes in 11/12 patients) Ear: • ADM successfully repaired tympanic membrane perforation in majority of patients in two studies • No difference in hearing results between ADM and autologous grafts Eye: • Successful periorbital soft tissue repair with ADM in a series of six patients. Scarring, wound contracture, and loss of volume potentially worse than with full-thickness skin grafts • Improvement in 105 cases (63 patients) with periorbital defects and no attributable complications • No significant difference between ADM and hard palate autographs in eyelid elevation after treatment for lower eyelid retraction Mouth: • ADM demonstrated high rate of epithelialization after intraoral reconstruction in one study • Rates of radiation and graft failure were higher and levels of inflammation, fibrosis, and elastic fibers were lower in the ADM group than the non-ADM group in another study. Palate: • Fistula repair rate 100% for ADM (AlloDerm) and 83.3% for historical controls in one study • Fistula recurrence rate following AlloDerm 10.9% (6 patients with large fistulas) in another study	• ADM used for a variety of head and neck reconstruction procedures. • Reported problems with ADM include resorption of the matrix, seroma, and thinning of the ADM under tension. • The authors suggest that adjustments to surgical techniques should be made to reduce the incidence and severity of these AEs. • There is a lack of high quality evidence regarding the safety and effectiveness of ADM from prospective, randomized controlled trials, and of studies with long-term follow-up.

Table A7: Summary of Findings of Included Systematic Reviews		
Author	**Main Study Findings**	**Author's Conclusions**
	Parotid: • One study reported resorption of ADM when used to fill the depression seen after parotidectomy; good incorporation of ADM in the face without decrease in volume over six months Pharynx • Small case series report successful oropharyngeal reconstruction with ADM following oncologic resection, with improved quality of life and function. • ADM added to local muscle flaps reduces reconstruction complications Dura: • In one retrospective review, 4/200 patients developed superficial wound infection after craniotomy and duraplasty with ADM, none had scarring or adhesion formation. • ADM demonstrated structural integrity following duraplasty. Treatment of facial paralysis: • Biomechanical evidence from one study suggested that Enduragen ADM had less elongation under stress than AlloDerm.	
Upper and Lower Extremity Wound Healing		
Iorio 2012[19]	Integra (8 studies): • Indications for use included: complex combat injuries or hand injuries with exposed tendon or bone, digital injuries, chronic lower extremity wounds including diabetic foot wounds and chronic calcaneal osteomyelitis • Rate of wound healing ranged from 87% to 100% • Repeat split-thickness skin graft required in 2/10 patients in one study • No other complications noted in any study GraftJacket (5 studies, including 3 RCTs): • Studied indications were various chronic diabetic wounds • Rate of wound healing (4 studies) ranged from 70% to 91% (vs. control group rates of 29% to 46% in 2 RCTs) • Closure area and depth, GraftJacket vs. control (1 RCT): 73.1% vs. 34.2% and 89.1% vs. 25.0%, respectively • Seroma: 1/20 (1 RCT) • No other complications noted in any study	• ADMs appear to be effective adjunctive treatment for chronic and traumatic injuries to the upper and lower extremities • ADM use allows for tissue repair even in the case of bone or tendon exposure. • No major risks were identified • Insufficient evidence to determine the ratio of vascularized tissue to surrounding tissue for optimal matrix incorporation • Further RCTs of wounds with exposed bone, tendon, or joint are required to demonstrate the comparative effectiveness of flap surgery, dermal template, and skin graft

Table A7: Summary of Findings of Included Systematic Reviews		
Author	**Main Study Findings**	**Author's Conclusions**
Breast Reconstruction		
Jansen 2011[20]	• Wound infection rates: 0% in 4 studies, ranged from 2.2% to 11% in 7 studies • Hematoma rates (7 studies): ranged from 0% to 6.7% • Seroma rates (8 studies): ranged from 0% to 9% • Partial flap necrosis (9 studies): ranged from 0% to 25% • Capsular contracture: 0% (6 studies; 10 to 21 month follow-up), 8% (1 study; 26 month follow-up) • Implant extrusion or loss (3 studies): ranged from 0% to 14% • Tissue expander exposure with salvage (3 studies): ranged from 0% to 8% • All reported measures of aesthetic outcomes were qualitative • Average length of stay (6 studies): 1 to 2 days	• AlloDerm for post-mastectomy alloplastic breast reconstruction is beneficial • Acute complications (wound infections, hematoma, seroma, skin necrosis) are minor and rates are comparable to those of two-stage breast reconstruction without AlloDerm • May be used in patients with a history of radiation • RCTs are required to study the use of AlloDerm for direct-to-implant vs. two-stage breast reconstruction
Perineal Reconstruction		
Foster 2012[21]	Biological mesh (5 studies) vs. tissue flap (6 or 7 studies): • Thirty-day mortality: 2/85 (2.4%) vs. 1/179 (0.5%) • Neoadjuvant radiotherapy: 51/85 (60%) vs. 147/162 (90.7%) • Perineal hernia: 3/85 (3.5%) vs. 7/179 (3.9%) • Wound healing complications, Clavinen-Dindo class I, II, or III: 28.2% vs. 31.8% • Chronic pain: minor, resolved spontaneously after biological mesh (2 studies); minimal pain after tissue flap (1 study) • Quality of life after reconstruction with biological mesh (1 study): comparable with a colorectal reference population • Length of hospital stay and operative time: few studies reported these outcomes; those that did suggested that these times were shorter for reconstruction with biological mesh than with tissue flap	• The authors suggest that perineal reconstruction with biological mesh or tissue flap are both effective methods for repair following extralevator abdominoperineal excision • Rates of early complications and mortality are low, but may not reflect true morbidity • Articles included in the review were of low quality and included few patients • Insufficient evidence to determine the superiority of one reconstruction method over another • High quality RCTs with long-term outcomes are required to confirm the clinical effectiveness and safety of biological mesh for this indication
Multiple Indications		
Jansen 2013[22]	Studies with level I (RCTs; n = 3) and level II evidence (cohort and ecological studies; n = 12): • 6 studies have positive outcomes for AlloDerm, 6 are neutral, 3 are negative All non-basic science studies (n = 225)	• Overall positive results for AlloDerm from a large number of studies with low quality of evidence • High quality RCTs are required to determine the clinical indications for which AlloDerm may be the most effective

Table A7: Summary of Findings of Included Systematic Reviews		
Author	**Main Study Findings**	**Author's Conclusions**
	• 85% of articles were level IV or V evidence (case series, case reports, expert opinion) • Positive outcomes for Alloderm: n = 157 (70%) • Neutral outcomes for Alloderm: n = 52 (23%) • Negative outcomes for Alloderm: n = 16 (7%)	

ADM = acellular dermal matrix; AE = adverse event; CI = confidence interval; CST = component separation technique; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MD = mean difference; mL = millilitre; OR = odds ratio; RR = relative risk; SMAS = superficial musculoaponeurotic system; vs. = versus

Table A8: Summary of Findings of Included Economic Evaluations	
Main Study Findings	**Author's Conclusions**
Chatterjee 2015[2]	
Base case: • Biological mesh vs. no biological mesh, ICUR = $15,002.90/QALY Sensitivity analyses: • Component separation with biological mesh was cost-effective when hernia recurrence rate without biological mesh was at least 16% (using Medicare reimbursement rates) • Biological mesh was not cost-effective for the average size of hernia defect (230 cm^2), until hernia recurrence rate without biological mesh was at least 24% (using retail costs) • Maximum cost of biological mesh for it to remain cost-effective at a WTP threshold of $50,000/QALY is $1813.53	From a third-party payer perspective, biological mesh is cost-effective for ventral hernia repair using component separation. It is not cost-effective from a private practice perspective due to the high retail costs of biological mesh.
Krishnan 2014[24]	
• Complication rates (from literature review) 30% and 34.5% with and without ADM Base case: • ICUR for ADM vs. no ADM = $264.20/QALY Sensitivity analyses (any complication rate without ADM; varying utility of mastectomy necrosis): • ADM is cost-effective at a WTP threshold of $50,000/QALY	From a third-party payer perspective, ADM is cost-effective for unilateral or bilateral implant-based breast reconstruction because of its long-term aesthetic benefits following successful procedures.
Krishnan 2013[25]	
• Complication rates (from literature review) 10.5% with ADM and 11% with autologous dermal flap Base case: • ICUR for ADM vs. autologous dermal flap = $261,720/QALY Sensitivity analyses: • At a WTP threshold of $50,000/QALY, ADM not cost-effective when complication rate of autologous dermal flaps was less than 20% • ADM cost-effective or strictly dominates when complication rate of autologous dermal flaps was over 20% • Mastectomy skin necrosis utility of 0, ICUR = $23,204.39/QALY; ADM not cost-effective if utility for mastectomy skin necrosis is 1 • ICUR of AlloDerm at retail cost = $5,101,506/QALY	From a third-party payer perspective, ADM for single-stage breast reconstruction is not cost-effective unless the complication rate of breast reconstruction with autologous dermal flap is greater than 20%.

ADM = acellular dermal matrix; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life year; WTP = willingness to pay

Table A9: Summary of Findings of Included Guidelines	
Evidence Summary	**Conclusions and Recommendations**
Bittner 2014 – International Endohernia Society[26]	
Biological meshes for laparoscopic repair of ventral and incisional hernias: • Use of non–cross-linked biological meshes for this indication has been associated with high rates of recurrence (Level 1b) • Cross-linked acellular porcine dermal collagen implants for this procedure do not have a higher recurrence rate than synthetic mesh (Level 3) • Biological meshes do not entirely prevent infection (Level 4) • Non–cross-linked biological meshes may be used for laparoscopic repair of ventral and incisional hernia in a potentially contaminated or infected surgical field if complemented with suture closure (Level 4)	*"Elective laparoscopic repair of incisional and ventral hernias should not be performed with the use of noncross-linked biological mesh with a bridging technique"* Grade A, pg. 385 *"Caution is advised in the use of biological meshes in a contaminated field"* Grade D, pg. 385 *"Laparoscopic repair of incisional and ventral hernias with non-cross-linked biological meshes in an infected or potentially contaminated surgical field may be a viable option if the hernia defect is closed primarily"* Grade D, pg. 385 *"Elective laparoscopic repair of incisional and ventral hernias with cross-linked biological meshes can be considered a reasonable surgical option"* Grade D, pg. 385
Maher 2013[1]	
• Anterior vaginal compartment pelvic organ prolapse is an indication for the use of biological mesh. • Cadaveric fascia lata has demonstrated a success rate of 81% to 100% for anterior compartment prolapse, cadaveric dermis has had a reported two year success rate ranging from 42% to 84%; there may be a risk of host-graft reactions • Reported success rates for porcine dermis have been variable, ranging from 64% to 100%; high recurrence rates of 50% have also been reported • 1 RCT of small intestine submucosa versus anterior colporrhaphy alone reported a lower objective failure rate with the biological mesh, and no difference between groups in dyspareunia and quality of life • A Cochrane meta-analysis showed lower objective failure rates with biological mesh versus anterior colporrhaphy alone • Three trials demonstrated no difference between biological mesh and native tissue repair alone in prolapse symptoms • 2 RCTs showed poorer objective outcomes with porcine graft overlay than with polypropylene mesh	• Results from meta-analyses have shown no improvement in subjective outcomes, but improvement in anatomical outcomes, for biological grafts compared with native tissue repair. (Grade B evidence) • There is conflicting evidence regarding the use of porcine dermis as a graft agent. There is limited data to support the use of small intestine submucosa as a graft agent. (Grade B evidence) • There is consistent, high quality evidence to support the use of polypropylene mesh, compared with a biological graft, with improved anatomical outcomes. (Grade A evidence)

Table A9: Summary of Findings of Included Guidelines	
Evidence Summary	**Conclusions and Recommendations**
NICE 2013[27]	
Autologous rectus fascial slings: • Higher objective cure rate, longer length of stay, no long-term difference in symptoms or satisfaction compared with periurethral silicone (1 RCT [EL 1+]) • Similar cure rates (2 RCTs) and less wound pain (1 RCT) compared with tension-free vaginal tape [EL 1+] • Similar cure and satisfaction rates compared with polypropylene mesh sling and vaginal wall sling [EL 1-] Open colposuspension vs. biological slings: • Open colposuspension vs. dura mater (1 RCT): cure rates 86% vs. 92%, more patients in the sling group with voiding or retention difficulty, higher incidence of rectocele in the colposuspension group [EL 1+] • Colposuspension vs. autologous rectus fascial sling: higher cure rates in sling group at 1 year (93% vs. 88% for colposuspension) [EL 1+] Porcine dermis sling vs. needle suspension (1 RCT): • Subjective cure rates at 2 years were 90% vs. 70% • Intraoperative blood loss and postoperative infection higher in the sling group MMK procedure • No evidence to suggest that the MMK procedure is significantly better than open colposuspension [EL 1+] • MMK procedure is not routine for clinical practice due to the serious adverse event osteitis pubis [EL 4]	*"If conservative management for SUI has failed, offer: synthetic mid-urethral tape, or open colposuspension, or autologous rectus fascial sling."* Pg. 272 *"Biological slings - Do not offer anterior colporrhaphy, needle suspensions, paravaginal defect repair and the Marshall–Marchetti–Krantz procedure for the treatment of [SUI]."* Pg. 272
AAOS 2009[28]	
• No relevant studies of sufficient quality were identified regarding biologic or interpositional grafts in patients with glenohumeral joint osteoarthritis. (Inconclusive recommendation) • There was insufficient high quality evidence to make a recommendation regarding the use of osteoarticular allograft, autograft, and interpositional soft tissue allograft in patients with glenohumeral joint osteoarthritis. (Inconclusive recommendation)	• The use of arthroscopic treatments, including biologic or interpositional grafts, in patients with glenohumeral joint osteoarthritis could not be recommended. (Pg. 22) • The use of biologic interposition arthroplasty, including osteoarticular allograft, autograft, and interpositional soft tissue allograft, in patients with glenohumeral joint osteoarthritis could not be recommended. (Pg. 23)

AAOS = American Association of Orthopaedic Surgeons; EL = evidence level; MMK = Marshall–Marchetti–Krantz; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; SUI = stress urinary incontinence

APPENDIX 5: Grading Scales of Included Evidence-Based Guidelines

Table A10: Grading Scales of Included Evidence-Based Guidelines

Levels of Evidence	Grading of Recommendations
Bittner 2014 – International Endohernia Society[26,29]	
1A. Systematic review of randomized clinical trials (RCTs) (with consistent results from individual studies) **1B.** RCTs (of good quality) **2A.** Systematic review of 2B studies (with consistent results from individual studies) **2B.** Prospective and comparative studies (or RCTs of poorer quality) **2C**. Outcome studies (e.g., analyses of large registries, population-based data) **3.** Retrospective and comparative studies, case–control studies **4.** Case series (i.e., studies without a control group) **5.** Expert opinion, animal or lab experiments	**A.** Consistent level 1 studies: strict recommendations ("standard," "surgeons must do it") **B.** Consistent level 2 or 3 studies or extrapolations from level 1 studies: less strict wording ("recommended," "surgeons should do it") **C.** Level 4 studies or extrapolations from level 2 or 3 studies: vague wording ("option," "surgeons can do it") **D.** Level 5 evidence or worryingly inconsistent or inconclusive studies at any level (no recommendation at all, described options)
Maher 2013[1]	
1. RCTs or systematic reviews **2.** Poor quality RCTs, prospective cohort studies **3.** Case series or retrospective studies **4.** Case reports	**A.** Consistent level 1 evidence **B.** Consistent level 2 and/or 3 studies, or "majority evidence" from RCTs **C.** Level 4 studies or "majority evidence" from level 2 or 3 studies or Delphi processed expert opinion **D.** "No recommendation possible"; evidence is inadequate or conflicting and expert opinion is derived without a formal analytical process such as Delphi
NICE 2013[27]	
1++ High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias **1+** Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias **1−** Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias **2++** High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability	**A.** At least one meta-analysis, systematic review or randomised controlled trial (RCT) that is rated as 1++, and is directly applicable to the target population; or a systematic review of RCTs or a body of evidence that consists principally of studies rated as 1+, is directly applicable to the target population and demonstrates overall consistency of results; or evidence drawn from a NICE technology appraisal **B.** A body of evidence that includes studies rated as 2++, is directly applicable to the target population and demonstrates overall consistency of results; or extrapolated evidence from studies rated

Table A10: Grading Scales of Included Evidence-Based Guidelines	
Levels of Evidence	**Grading of Recommendations**
that the relationship is causal **2+** Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal **2−** Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal **3** Non-analytical studies (for example case reports, case series) **4** Expert opinion, formal consensus	as 1++ or 1+ **C.** A body of evidence that includes studies rated as 2+, is directly applicable to the target population and demonstrates overall consistency of results; or extrapolated evidence from studies rated as 2++ **D.** Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+; or formal consensus **D (GPP).** A GPP is a recommendation for best practice based on the experience of the guideline development group
AAOS 2009[28]	
I. High quality RCT with statistically significant difference or no statistically significant difference but narrow confidence intervals; systematic review of Level I RCTs (and study results were homogeneous) **II.** Lesser quality RCTs (e.g., < 80% follow-up, no blinding, improper randomization); prospective comparative study; systematic review of Level II studies or Level I studies with inconsistent results **III.** Case-control study; retrospective comparative study; systematic review of Level III studies **IV.** Case series **V.** Expert opinion	**Strong.** Evidence is based on two or more "High" strength studies with consistent findings for recommending for or against the intervention. A Strong recommendation means that the benefits of the recommended approach clearly exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a strong negative recommendation), and that the strength of the supporting evidence is high. **Moderate.** Evidence from two or more "Moderate" strength studies with consistent findings, or evidence from a single "High" quality study for recommending for or against the intervention. A Moderate recommendation means that the benefits exceed the potential harm (or that the potential harm clearly exceeds the benefits in the case of a negative recommendation), but the strength of the supporting evidence is not as strong. **Limited.** Evidence from two or more "Low" strength studies with consistent findings, or evidence from a single Moderate quality study recommending for or against the intervention or diagnostic. A Limited recommendation means the quality of the supporting evidence that exists is unconvincing, or that well-conducted studies show little clear advantage to one approach versus another. **Inconclusive.** Evidence from a single low quality study or conflicting findings that do not allow a recommendation for or against the intervention. An Inconclusive recommendation means that there is a lack of compelling evidence resulting in an unclear balance between benefits and potential harm.

Table A10: Grading Scales of Included Evidence-Based Guidelines	
Levels of Evidence	**Grading of Recommendations**
	Consensus. The supporting evidence is lacking and requires the work group to make a recommendation based on expert opinion by considering the known potential harm and benefits associated with the treatment. A Consensus recommendation means that expert opinion supports the guideline recommendation even though there is no available empirical evidence that meets the inclusion criteria.

GPP = good practice point; RCT = randomized controlled trial

APPENDIX 6: Additional References of Potential Interest

Randomized Controlled Trials Not Included in Systematic Reviews (published after study selection for included systematic reviews, or irrelevant indication for included systematic reviews)

Hernia Repair

Koetje JH, Irvine T, Thompson SK, Devitt PG, Woods SD, Aly A, et al. Quality of Life Following Repair of Large Hiatal Hernia is Improved but not Influenced by Use of Mesh: Results From a Randomized Controlled Trial. World J Surg. 2015 Jun;39(6):1465-73.

Bellows CF, Shadduck P, Helton WS, Martindale R, Stouch BC, Fitzgibbons R. Early report of a randomized comparative clinical trial of Strattice reconstructive tissue matrix to lightweight synthetic mesh in the repair of inguinal hernias. Hernia. 2014 Apr;18(2):221-30.

Shen YM, Chen J, Tian ML, Yang S, Liu SJ, Wang MG. Lichtenstein repair of indirect inguinal hernias with acellular tissue matrix grafts in adolescent patients: a prospective, randomized, controlled trial. Surg Today. 2014 Mar;44(3):429-35.

Abdominal Wall Reconstruction

Fleshman JW, Beck DE, Hyman N, Wexner SD, Bauer J, George V, et al. A prospective, multicenter, randomized, controlled study of non-cross-linked porcine acellular dermal matrix fascial sublay for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies. Dis Colon Rectum. 2014 May;57(5):623-31.

Sarr MG, Hutcher NE, Snyder S, Hodde J, Carmody B. A prospective, randomized, multicenter trial of Surgisis Gold, a biologic prosthetic, as a sublay reinforcement of the fascial closure after open bariatric surgery. Surgery. 2014 Oct;156(4):902-8.

Breast Reconstruction

Mendenhall SD, Anderson LA, Ying J, Boucher KM, Liu T, Neumayer LA, et al. The BREASTrial: stage I. Outcomes from the time of tissue expander and acellular dermal matrix placement to definitive reconstruction. Plast Reconstr Surg. 2015 Jan;135(1):29e-42e.

Hanna KR, DeGeorge BR, Jr., Mericli AF, Lin KY, Drake DB. Comparison study of two types of expander-based breast reconstruction: acellular dermal matrix-assisted versus total submuscular placement. Ann Plast Surg. 2013 Jan;70(1):10-5.

McCarthy CM, Lee CN, Halvorson EG, Riedel E, Pusic AL, Mehrara BJ, et al. The use of acellular dermal matrices in two-stage expander/implant reconstruction: a multicenter, blinded, randomized controlled trial. Plast Reconstr Surg [Internet]. 2012 Nov [cited 2015 Aug 10];130(5 Suppl 2):57S-66S. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4100590

Nahabedian MY. Discussion: The use of acellular dermal matrices in two-stage expander/implant reconstruction: a multicenter, blinded, randomized controlled trial. Plast Reconstr Surg. 2012 Nov;130(5 Suppl 2):67S-9S.

Mucogingival Surgery

Basegmez C, Karabuda ZC, Demirel K, Yalcin S. The comparison of acellular dermal matrix allografts with free gingival grafts in the augmentation of peri-implant attached mucosa: a randomised controlled trial. Eur J Oral Implantol. 2013;6(2):145-52.

Gholami GA, Saberi A, Kadkhodazadeh M, Amid R, Karami D. Comparison of the clinical outcomes of connective tissue and acellular dermal matrix in combination with double papillary flap for root coverage: A 6-month trial. Dent Res J (Isfahan) [Internet]. 2013 Jul [cited 2015 Aug 10];10(4):506-13. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3793415

Thombre V, Koudale SB, Bhongade ML. Comparative evaluation of the effectiveness of coronally positioned flap with or without acellular dermal matrix allograft in the treatment of multiple marginal gingival recession defects. Int J Periodontics Restorative Dent. 2013 May;33(3):e88-e94.

Hashemi HM, Parhiz A, Ghafari S. Vestibuloplasty: allograft versus mucosal graft. Int J Oral Maxillofac Surg. 2012 Apr;41(4):527-30.

Sadat MS, Ayoubian N, Eslami MM. A comparative 6-month clinical study of acellular dermal matrix allograft and subepithelial connective tissue graft for root coverage. J Dent (Tehran) [Internet]. 2010 [cited 2015 Aug 10];7(3):156-64. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3184755

Empty Nose Syndrome

Saafan ME. Acellular dermal (alloderm) grafts versus silastic sheets implants for management of empty nose syndrome. Eur Arch Otorhinolaryngol. 2013 Feb;270(2):527-33.

Rotator Cuff Repair

Barber FA, Burns JP, Deutsch A, Labbe MR, Litchfield RB. A prospective, randomized evaluation of acellular human dermal matrix augmentation for arthroscopic rotator cuff repair. Arthroscopy. 2012 Jan;28(1):8-15.

Stress Urinary Incontinence

Guerrero KL, Emery SJ, Wareham K, Ismail S, Watkins A, Lucas MG. A randomised controlled trial comparing TVT, Pelvicol and autologous fascial slings for the treatment of stress urinary incontinence in women. BJOG. 2010 Nov;117(12):1493-502.

Urethroplasty

Jamal JE, Kellner DS, Fracchia JA, Armenakas NA. A randomized prospective trial of primary versus AlloDerm closure of buccal mucosal graft harvest site for substitution urethroplasty. Urology. 2010 Mar;75(3):695-700.

Clinical Practice Guidelines – Unclear Methodology

Martin L, O'Donoghue JM, Horgan K, Thrush S, Johnson R, Gandhi A, et al. Acellular dermal matrix (ADM) assisted breast reconstruction procedures: joint guidelines from the Association of Breast Surgery and the British Association of Plastic, Reconstructive and Aesthetic Surgeons. Eur J Surg Oncol. 2013 May;39(5):425-9.

Sartelli M, Coccolini F, van Ramshorst GH, Campanelli G, Mandala V, Ansaloni L, et al. WSES guidelines for emergency repair of complicated abdominal wall hernias. World J Emerg Surg [Internet]. 2013 [cited 2015 Jul 21];8(1):50. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4176144